IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Applicant:	Ebrahim ZANDI, *et al.*
Title:	COMPOSITION AND METHOD FOR RECONSTITUTING IkB KINASE IN YEAST AND METHODS OF USING SAME
Appl. No.:	10/079,949
Filing Date:	2/19/2002
Office:	Prouty, Rebecca E.
Art Unit:	1652
Confirmation Number:	6542

CERTIFICATE OF ELECTRONIC TRANSMISSION
I hereby certify that this paper is being electronically transmitted to the **United States Patent and Trademark Office, Alexandria, Virginia** via EFS-Web on the date below.

Laura Johnson
(Printed Name)

Laura Johnson
(Signature)

September 3, 2010
(Date of Transmission)

REPLY BRIEF

Mail Stop Appeal Brief - Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Under the provisions of 37 C.F.R. § 41.41, this Reply Brief is submitted in response to the Examiner's Answer dated July 6, 2010. The due date for filing this Reply Brief is therefore September 6, 2010. Accordingly, this Reply Brief is timely filed.

Although Appellants believe no fee is required, authorization is hereby given to charge any deficiency (or credit any balance) to the undersigned deposit account 19-0741.

REAL PARTY IN INTEREST

The real party in interest is the University of Southern California. An assignment of rights from the inventors and Appellants, Ebrahim Zandi and Beth Schomer Miller, to the University of Southern California was recorded at the United States Patent and Trademark Office on May 31, 2002, at Reel 012943 and Frame 0139.

RELATED APPEALS AND INTERFERENCES

None.

STATUS OF CLAIMS

Canceled claims: 1, 3, 4, 8-16, 20 and 24-41.

Pending claims: 2, 5-7, 17-19, 21-23 and 42.

Withdrawn claims: No claims are withdrawn.

Rejected claims: 2, 5-7, 17-19, 21-23 and 42.

Appealed claims: 2, 5-7, 17-19, 21-23 and 42.

Allowed claims: No claims are allowed.

Objected claims: No claims are objected to.

The pending claims are presented in Claims Appendix of this Brief.

STATUS OF AMENDMENTS

Appellants filed an amendment and a Request for Continued Examination on July 28, 2009 in response to the Final Office Action dated June 9, 2009. In reply, a Final Office Action was issued on September 2, 2009. Appellants filed a supplemental amendment on December 1, 2009, which was refused entry by the Office in an Advisory Action issued on December 29, 2009.

The appealed claims and their status identifiers reflect those submitted in the Amendment and Reply filed July 28, 2009, and which were pending before the Examiner when the Final Office Action was issued on September 2, 2009.

SUMMARY OF CLAIMED SUBJECT MATTER

The claimed subject matter, in general, relates to preparing an activated and thus active and biologically functional IKK protein complex in yeast by transforming yeast with sequences encoding the three subunits of the IKK protein complex - IKKα, IKKβ, and IKKγ and then separating the activated IKK protein complex from the yeast. As of the effective filing date of the present application, it was believed that activation of the IKK complex requires the TNF-α and NF-κB signaling pathways (page 3, line 12 to page 4, line 12), which are present in mammalian cells but absent in yeast (page 6, lines 6 to 7). Accordingly, one of skill in the art at the time the invention was made would not have expected that an activated IKK complex could be prepared in yeast, which lacks the TNF-α and NF-κB signaling pathways.

The present invention, however, provides a ready solution to this problem by demonstrating that the subunit IKKγ regulates autophosphorylation of the subunit IKKβ leading to self-activation of the IKK complex. *See*, Experimental Example 2 (page 15, line 29 to page 17, line 19, in particular page 16, lines 20 to 21) and Summary of Invention (page 7, lines 6 to 14). Therefore, an activated IKK complex can be prepared in yeast by simply expressing the subunit proteins which would then undergo autophosphorylation and self-activation, without having to reconstitute the TNF-α and NF-κB signaling pathways in the yeast. This surprising discovery then is the basis of the presently claimed method of preparing substantially homogenous, biologically functional and activated IKK protein complex in yeast.

Claims 2, 5-7, 17-19, 21-23 and 42 remain pending and are subject to appeal. The present application presents two independent claims, namely, claims 2 and 42. Claims 5-7, 17-19 and 21-23 depend from claim 2 or claim 42.

Independent claim 2 is directed to a method for preparing substantially homogenous (page 20 line 31 to page 21 line 2), biologically functional (page 10, lines 27-28) and activated (page 7, lines 8-9) IKK protein complex. The method entails

transforming a yeast with an IKK subunit gamma (γ) gene, an IKK subunit alpha (α) gene and an IKK subunit beta (β) gene (page 6, lines 27-29). and growing the yeast (page 6, line 30) allowing production of active and biologically functional IKK protein complex in the yeast. Subsequently, substantially homogenous IKK protein complex is separated from the yeast (page 7, line 1) in a fully active and biologically functional state requiring no further processing to achieve activity and functionality.

Independent claim 42 is directed to a method for preparing substantially homogenous (page 20 line 31 to page 21 line 2), biologically functional (page 10, lines 27-28) and activated (page 7, lines 8-9) IKK protein complex. As prescribed by claim 42, the method entails transforming a yeast with an IKK subunit gamma (γ) gene, an IKK subunit alpha (α) gene and an IKK subunit beta (β) gene (page 6, lines 27-29) and growing the yeast (page 6, line 30). In the yeast, IKK protein complex is produced and autophosphorylated at a T loop of an IKK subunit beta (β) (page 7, lines 6-9). By separating the autophosphorylated and thus activated IKK protein complex from the yeast(page 7, line 1) substantially homogenous, biologically functional and activated IKK protein complex is prepared.

Claim 5, dependent on claim 2 or 42, is directed to inclusion of a tag (page 6, line 28) to the IKK gene sequences.

Claim 6, dependent on claim 2 or 42, is directed to defining the tag to be selected from selected from the group consisting of myc, HA, FLAG and 6his (page 22, Table 1).

Claim 7, dependent on claim 2 or 42, is directed to inclusion of an inducible promoter or a constitutive promoter (page 12, lines 9-12) to the IKK gene sequences.

Claim 17, dependent on claim 2 or 42, is directed to defining the yeast as *Saccharomyces cerevisiae* (page 12, line 1).

Claim 18, dependent on claim 2 or 42, is directed to defining one or more of the IKK gene being a mammalian IKK gene (page 8, line 10 and the originally filed claim 18).

Claim 19, dependent on claim 2 or 42, is directed to defining one or more of the IKK gene being a human IKK gene (page 8, line 10).

Claim 21, dependent on claim 2 or 42, is directed to defining that the yeast is grown in selective liquid media (page 6, line 30).

Claim 22, dependent on claim 2 or 42, is directed to defining that one or more of the IKK gene encodes a wild-type IKK subunit protein (page 10, line 4).

Claim 23, dependent on claim 2 or 42, is directed to defining that one or more of the IKK gene encodes a mutated IKK subunit protein (page 9, line 5-21).

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The claims in this application stand rejected as follows:

Claims 2, 5-7, 17-19, 21-23 and 42 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Rothwarf *et al.* (1998) *Nature* 395:297-300 (hereinafter "Rothwarf") in view of Traincard *et al.* (1999) *J. Cell Science* 112:3529-35 (hereinafter "Traincard") and Epinat *et al.* (1997) Yeast 16:599-612 (hereinafter "Epinat").

Briefly and for the sake of completeness, the Office alleged that Rothwarf discloses that NIK and MEKK1 phosphorylate IKK *in vitro* (*i.e.*, in the absence of any cellular context) and therefore it is obvious that NIK and MEKK1 can phosphorylate IKK in yeast. Additionally, the Office alleged that Traincard discloses that yeast does not have homologs of any member of the NF-κB signaling system. Further, the Office alleged that Epinat discloses that yeast is a convenient host for reconstitution of the NF-κB system since it does not contain any endogenous NF-κB activity.

ARGUMENT

Pursuant to 37 C.F.R. § 41.41, Appellants respond to certain comments made in the Examiner's Answer dated July 6, 2010 ("the Answer").

A. The Examiner misinterpreted the claimed invention

Central to the Examiner's arguments in the Answer is the Examiner's incorrect interpretation of the claim language.

Claim 1 recites a "method for preparing substantially homogenous, biologically functional and activated IKK protein complex *comprising* transforming a yeast with ... and growing said yeast and separating said IKK protein complex from said yeast."

First, the "IKK protein complex" that is separated from the yeast is the "substantially homogenous, biologically functional and activated IKK protein complex" which provides the antecedent basis. In this context, the claimed method, in view of the transitional phrase "comprising", includes at least the following steps:

(1) transforming a yeast with the IKK genes;

(2) growing the yeast; and

(3) separating substantially homogenous, biologically functional and activated IKK protein complex from the yeast.

In the Answer, the Examiner repeatedly stated that by virtue of the phrase "comprising", the claims "thus do not exclude additional steps to activate recombinantly expressed IKK complex by methods" known in the art such as *in vitro* activation by NIK and/or MEKK1. The Answer at page 9, lines 12-14, emphasis added. *See* also, *id.* at page 8, lines 9-10, page 10, lines 13-18 and page 15, lines 2-6. Accordingly, the Examiner interpreted the claim to include the following steps:

(1) transforming a yeast with the IKK genes;

(2) growing the yeast;

(3) separating non-activated IKK protein complex from the yeast; and

(4) activating the non-activated IKK protein complex *in vitro*.

This interpretation imports a new step from what is recited in the claims and, more importantly, changes a step from those included in the claimed invention. More specifically, the claimed invention entails separating an activated IKK protein complex from the yeast which requires that the complex be activated in the yeast, whereas the Examiner interpreted the step to mean separating a non-activated IKK protein complex from the yeast and then performing additional steps to activate the complex. Therefore, the Examiner interpretation is inconsistent with the plain language of the claims.

With this perspective, Appellants will demonstrate that the Examiner's rejection of the pending claims should be withdrawn because they are either based on misinterpretation of the claims or the cited art.

B. The Examiner based the rejections on misinterpretation of the claims or misreading of the cited art

In the Answer, the Examiner set forth three scenarios, all of which were allegedly encompassed by the claimed invention and provided basis for the invention being obviousness in view of the cited art.

In scenario one, the Examiner contended, "[o]ne of skill in the art would reasonably expect that coexpression of the three subunits together in yeast would produce a complex that would have the basal level of kinase activity demonstrated by the unstimulated cells of Rothwarf *et al.*" *Id.* at page 7, line 21 to page 8, line 2, emphasis added. Appellants submit that this is actually not encompassed by the claimed invention.

The claimed invention is directed to a method of preparing an activated IKK protein complex in a yeast system. As demonstrated in the Amendment and Reply filed on July 29, 2009, "activated" refers to "a state of being more then usually active." Page 11, third full paragraph. By contrast, "basal" refers to "of, relating to, or being essential for maintaining the fundamental vital activities of an organism : MINIMAL." *Id.* Therefore, an IKK protein complex with basal level of activity is clearly not an activated

IKK protein complex, as prescribed by the claimed invention. Clearly, the Examiner's scenario one does not fall into the scope of the claimed invention.

Then, in scenario two, the Examiner contended that "even if" scenario one is "in fact proved not to be the case a skilled artisan would have clearly expected that active complex could be produced by lysing the yeast following expression and addition of exogenous NIK or MEKK1 to the lysate." The Answer at page 8, lines 2-5. By virtue of the "proved not to be the case" premise, the Examiner's scenario two requires a step of separating a non-activated IKK protein complex. As demonstrated above, this step is not encompassed by the claimed invention. Therefore, the Examiner's argument in scenario two is also misplaced.

Moreover, the Examiner's scenario three envisions "coexpressing NIK or MEKK1 in the yeast host" to activate the IKK protein complex "as Rothwarf *et al.* clearly teach that these proteins activate the IKK complex *in vitro*." *Id.* at page 8, lines 6-8. As will be demonstrated below, Rothwarf *et al.* actually do not teach that **any** NIK or MEKK1 activates IKK complex *in vitro*. What Rothwarf *et al.* actually teach is that the NIK or MEKK1 protein was expressed in human cells first and such expressed NIK or MEKK1 protein became activated in the human cells before phosphorylating IKK.

In the Appeal Brief, Appellants submit that Rothwarf *et al.*, through the cited reference Ling *et al.*, discloses that NIK was first expressed in a human cell line, 293 cells, and then was isolated from the cells before it was used to activate IKK. Appeal Brief at page 12, last paragraph. Ling *et al.* further discloses that, in an improved understanding of the NF-κB pathway illuminated by the findings reported therein, NIK becomes activated before activating IKK. *Id.* at page 13, lines 1-2.

In the Answer, the Examiner disagreed, contending that nothing in Ling *et al.* "indicates that the 293 cells were grown in the presence of TNF-α or any other known activator of the TNF-α and NF-κB signal pathways" therefore NIK would not have been activated. The Answer at page 13, lines 2-4. Appellants submit that the Examiner's

argument is misplaced and also, at first glance, appears to contradict the Examiner's basis for rejection.

First, Appellants respectfully submit that the cited art does not state that the presence of TNF-α or any other known activator of the TNF-α and NF-κB signal pathways is required for activation of NIK. Therefore, there is no support for the statement that these activators are required for activation of NIK.

Further, the Examiner has repeatedly argued that the IKK protein complex can be activated by mere coexpression of NIK, not requiring any external activators. Yet, by the same token, the Examiner stated that the mere existence of upstream activators of NIK, which are inherently coexpressed in human cells, is not sufficient to activate NIK in the absence of external activators such as TNF-α.

The Examiner's argument also contradicted Ling *et al.*'s teaching that NIK is activated before activating IKK. Therefore, at the minimum, the prior art teaches that IKK protein complex can be activated by NIK protein that is expressed in human cells. The Examiner failed to show that the skilled artisan would have expected that an NIK protein expressed in yeast would have the same activity as an NIK protein expressed in human. Therefore, the Office has not presented a *prima facie* case of obviousness.

Finally, with respect to claim 42, the Examiner contended that the cited art suggests that phosphorylation of IKK-β is at Ser177 (*id.* at page 8, lines 19-22) and thus renders claim 42 obvious. Appellants respectfully disagree.

In addition to the elements discussed in the Answer, claim 42 also prescribes that the IKK protein complex is autophosphorylated. At a minimum, the Examiner failed to consider this element and thus failed to consider every limitation of the claimed invention, as required by *MPEP § 1245*.

Appellants note that later on in the Answer and in response to Appellants' earlier argument regarding the autophosphorylation element, the Examiner stated that "[w]hether this phosphorylation is produced by IKK-β (i.e., autophosphorylation) or by

NIK (i.e., a heterologous kinase), the IKK complex produced is structurally identical and meets the limitation recited in claim 42." *Id.* at page 15, lines 14-18. Appellants respectfully disagree with the Examiner's interpretation of claim 42.

Claim 42 prescribes that the IKK protein complex autophosphorylates and then substantially homogenous, biologically functional and activated IKK protein complex is separated from the yeast. Hence, the IKK protein complex separated from the yeast is the autophosphorylated IKK protein complex. Therefore, not only does autophosphorylation constitute a natural consequence of earlier steps of the claimed invention, *i.e.*, transforming the yeast with IKK genes and growing the yeast, it is also an essential and structural element of one step of the claimed method. Accordingly, without considering the element, a *prima facie* case was not presented.

C. Responses to the Examiner's other arguments in response to the Appeal Brief

In the Appeal Brief, Appellants stated that the claimed invention is based on the unexpected finding that IKK-γ regulates autophosphorylation of IKK-β, leading to self-activation of the IKK complex.

In response, the Examiner contended that this was not unexpected in view of U.S. Patent 6,864,355. *Id.* at page 9, lines 3-5. The Answer, however, does not specify how this was not unexpected. A more detailed explanation, Appellants believe, is provided at page 13, second to last line to page 14, line 3, where the patent states that "IKK-β becomes auto-phosphorylated, basally active and refractory to TNF-α induced signals." Emphasis added.

It is therefore Appellants' position that the Examiner only showed that it would have been expected to prepare autophosphorylated IKK protein complex that has basal activity. The prescribed invention, however, is directed to preparing activated IKK protein complex in a yeast without the need for additional steps or modifications. As demonstrated earlier, an activated IKK protein complex does not encompass an IKK

protein complex that only has a basal level of activity. Therefore, the rejection is in error and reversal is respectfully requested.

Conclusions

In the Answer, the Examiner alleged that the claimed invention, by virtue of the transitional phrase "comprising" does not exclude an additional step of activating a non-activated IKK protein complex *in vitro* by NIK or MEKK1. However, by including such an additional step, the Examiner necessarily interpreted the separating step of the claimed invention to mean separating a non-activated IKK protein complex from the yeast and then performing additional steps to obtain the complex. By contrast, in view of the antecedent basis of the phrase "said IKK protein complex", it is clear that in the method prescribed by the present claims, activated IKK protein complex is separated from the yeast, contrary to the Examiner's interpretation. Therefore, the Examiner's misinterpretation the claimed invention has formed the basis for the grounds for rejection.

Another line of errors in the Answer arises from the Examiner's failure to recognize, in spite of Appellants' attempts to clarify, the distinction between "basal level of activity" and "activated activity". The cited art, the Examiner alleged, teaches autophosphorylation of IKK leading to basal activity of the IKK protein complex. The claimed invention, by contrast, is based on the unexpected finding that the IKK protein complex autophosphorylates and activates itself.

Yet another error included in the Answer results from the Examiner's insistence of the misreading of the prior art. The Examiner recognized that *in vitro* does not mean in the absence of any cellular context which the Examiner stated explicitly early on. Nevertheless, the Examiner failed to recognize that expression of NIK in a human cell plays any role in the activation of NIK, which the prior art suggests is required for NIK to activate IKK, in spite of the explicit teaching of the very prior art reference and contradicting her own rational in rejecting the claimed invention.

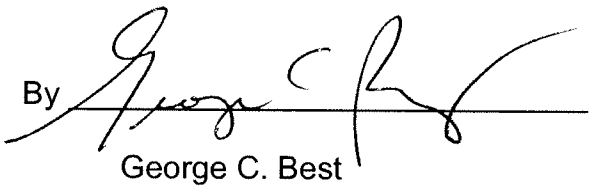
Finally, claim 42 entails a step of separating from the yeast an IKK protein complex that is already autophosphorylated and activated from the yeast. Therefore, autophosphorylation constitutes an essential feature of the step. The Examiner, however, failed to consider the autophosphorylation element of the claim thereby violating PTO's own rules set forth in *MPEP § 1245.*

For at least the reasons described above, Appellants respectfully submit that the Examiner's reasoning in rejecting the claimed invention under 35 U.S.C. § 103 is misplaced and withdrawal of the rejection is warranted.

Accordingly, Appellants respectfully request withdrawal of the rejection.

Respectfully submitted,

Date: September 3, 2010

By 

FOLEY & LARDNER LLP
Customer Number: 38706
Telephone: (650) 251-1129
Facsimile: (650) 856-3710

George C. Best
Attorney for Applicants
Registration No. 42,322

Alex Y. Nie
Attorney for Applicants
Registration No. 60,523

Antoinette F. Konski
Attorney for Applicant
Registration No. 34,202

CLAIMS APPENDIX

1. (Canceled)

2. (Previously Presented) A method for preparing substantially homogenous, biologically functional and activated IKK protein complex comprising transforming a yeast with an IKK subunit gamma (γ) gene and an IKK subunit alpha (α) gene and an IKK subunit beta (β) gene and growing said yeast and separating said IKK protein complex from said yeast thereby preparing substantially homogenous, biologically functional and activated IKK protein complex.

3. (Canceled)

4. (Canceled)

5. (Previously Presented) The method of claim 2 or 42, wherein one or more of said IKK subunit (γ) gene, or IKK subunit (α) gene or IKK subunit (β) gene further comprises a sequence encoding a tag.

6. (Previously Presented) The method of claim 5, wherein said tag is selected from the group consisting of myc, HA, FLAG and 6his.

7. (Previously Presented) The method of claim 2 or 42, wherein one or more of said IKK subunit (γ) gene, or IKK subunit (α) gene or IKK subunit (β) gene is linked to an inducible promoter or a constitutive promoter.

Claims 8 –16. (Canceled).

17. (Previously Presented) The method of claim 2 or 42, wherein said yeast is Saccharomyces cerevisiae.

18. (Previously Presented) The method of claim 2 or 42, wherein one or more of said IKK subunit (γ) gene, or IKK subunit (α) gene or IKK subunit (β) gene is a mammalian IKK gene.

19. (Previously Presented) The method of claim 18, wherein one or more of said mammalian IKK subunit (γ) gene, or mammalian IKK subunit (α) gene or mammalian IKK subunit (β) gene is a human.

20. (Canceled)

21. (Previously Presented) The method of claim 2 or 42, wherein said yeast is grown in selective liquid media.

22. (Previously Presented) The method of claim 2 or 42, wherein one or more of said IKK subunit (γ) gene, or IKK subunit (α) gene or IKK subunit (β) gene encodes a wild-type IKK subunit protein.

23. (Previously Presented) The method of claim 2 or 42, wherein one or more of said IKK subunit (γ) gene, or IKK subunit (α) gene or IKK subunit (β) gene encodes a mutated IKK subunit protein.

Claims 24 – 41. (Canceled)

42. (Previously Presented) A method for preparing substantially homogenous, biologically functional and activated IKK protein complex comprising transforming a

yeast with an IKK subunit gamma (γ) gene and an IKK subunit alpha (α) gene and an IKK subunit beta (β) gene and growing said yeast and separating said IKK protein complex from said yeast, wherein the IKK protein complex is autophosphorylated at a T loop of an IKK subunit beta (β) thereby preparing substantially homogenous, biologically functional and activated IKK protein complex.

EVIDENCE APPENDIX

None.

RELATED PROCEEDINGS APPENDIX

As indicated above, Appellant is unaware of any other prior or pending appeals, interferences or judicial proceedings which may be related to, directly affect or be directly affected by or have a bearing on the decision in this application. Accordingly, no decision has been rendered by a court or the Board in a related proceeding.